FDA Executive Summary

Prepared for the
September 21, 2012 Meeting of the
Orthopaedic and Rehabilitation Devices Panel

Petition to Request Classification for
Posterior Cervical Pedicle and Lateral Mass
Screw Spinal Systems

Table of Contents

List of Figures

List of Tables

1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the FDA is convening the Orthopaedic and Rehabilitation Devices Advisory Panel (the panel) for the purpose of securing recommendations regarding the classification of cervical pedicle and lateral mass screw spinal systems, as discussed in a petition submitted by the Orthopedic Surgical Manufacturers Association (OSMA) (see Appendix A). Specifically, the panel will be asked to provide recommendations regarding the proposed placement of posterior pedicle and lateral mass screws for use in the cervical spine into Class II.

This petition was originally submitted as a response to the FDA's August 2009 515(i) request for information for pedicle screw use in the thoracolumbosacral spine, but at the request of the Agency, was filed separately for review.

1.1. Current Regulatory Pathways

Cervical screws were determined to be devices legally marketed in the US before passage of the Medical Device Amendments on May 28, 1976 (i.e., preamendment devices). However, cervical screws have not been previously discussed by the panel for the purpose of determining the appropriate classification; therefore, these devices remain unclassified.[1] In contrast, occipital-cervico-thoracic (OCT) systems are currently cleared via the 510(k) pathway and considered to be Class II devices that are intended to be used as an adjunct to fusion of the OCT junction as well as the cervical spine. In these systems, screw use is limited to the occiput and the thoracic spine (T1-T3).

1.2. Device Description

Modern posterior cervical instrumentation most commonly involves the use of a rod and screw fixation system that can span from the occiput to the upper thoracic spine. Cervical lateral mass and pedicle screws can serve as the primary anchor points in these OCT devices, which have a variety of different components and configurations to accommodate individual patient anatomy. Nearly all OCT systems consist of an anchor via screws (i.e., occipital, lateral mass, and pedicle), longitudinal members (e.g., plates, rods, and/or hybrid plate/rod configurations) and optional transverse connectors. The screws (anchors) form the bone-implant interface, the longitudinal members connect the anchor points, and transverse connectors link the longitudinal members for additional stability. Finally, an interconnection mechanism (e.g., offset connector, nuts, screws, sleeves, or bolts) is utilized to link the anchor and longitudinal member.

1.2.1. Screw Types

Various types of screws are used to immobilize and stabilize segments of the cervical spine and have a wide range of features that provide adaptability to a given patient's anatomy. These features include variations in screw or tulip head design, threading options, and assembly features to ease implantation.

[1] There is only a single, cleared 510(k) that includes posterior cervical screw fixation (K062254, Medtronic Axis Fixation System).

Current posterior OCT systems most commonly utilize screws as the bone anchor component in the occiput. In the cervical spine, screws placed into the pedicles and lateral masses are currently the predominant technique for achieving fixation and have replaced the use of wires and hooks in most clinical situations. However, screw use in the cervical spine is currently unclassified by the FDA.

It is important to note that this petition does not consider all known uses of cervical screw fixation. The FDA has knowledge regarding these additional methods of screw fixation, but the scope of this review pertains specifically to consideration of cervical screws that are utilized as an anchor in a multi-component system that also includes use of a longitudinal member. Specifically excluded from consideration is the use of screws which achieve intrasegmental fixation (i.e., "osteosynthesis"), also described in literature for use in treatment of specific cervical fractures (e.g., C2 Hangman's type fractures), which is not for the purposes of fusion across a spinal motion segment. Additionally, screw fixation techniques that are not required to be used in combination with longitudinal members, such as transfacet screws, are excluded from this discussion. Finally, this petition does not address bone screws cleared for general use in other parts of the body, such as the bones of the upper or lower extremities, nor does it address screws cleared for use in the extremities that are subsequently used by surgeons in the spine.

1.2.2. Plate Components

The original devices available for use with screws to achieve fixation in the posterior aspect of the occiput and cervical spine were screw-plate systems. In contemporary OCT systems, occipital anchors most commonly include varying shapes and sizes of metallic plates or offset screw-rod connectors, which are used primarily for attachment to the occiput via bone screws. These occipital anchors can also serve as an anchor point for rods that span the cervicothoracic spinal region. In the cervical region (C1-C7), plate systems have largely been replaced by cervical screw-rod systems due to ease of use considerations.

1.2.3. Longitudinal and Connecting Elements

Current posterior cervical screw fixation systems include varying sizes and configurations of rods, which may be extended proximally to connect occipital anchor points (e.g., plates) and distally to connect to pedicle screw anchors in the thoracic region, in addition to achieving fixation via screws in the cervical region. Stability of these screw-rod constructs may be enhanced by placement of transverse connectors ("cross-linking"). Further versatility is provided by various rod-rod connecting options, such as offset and in-line longitudinal connectors.

2. Regulatory History

A brief summary of the regulatory history for spinal pedicle screw systems is provided within this section. Of note, the regulatory history is almost entirely focused on use of these systems in the thoracolumbosacral spine.

2.1. 1993 Classification Panel Meeting

In 1993, the FDA requested data related to all pedicle screw fixation systems, which were unclassified at the time. The 1993 classification panel meeting was the first in which postamendments pedicle screw fixation systems were discussed. Specifically, the panel discussed the concept of a historical cohort study, which would provide clinical information on the use of pedicle screw fixation in thoracic, lumbar, and sacral fusions.

2.2. 1994 Classification Panel Meeting

This second classification panel meeting was held in order to present a compilation of data regarding the use of pedicle screw fixation, primarily in the thoracolumbar spine. Based on this information, the panel agreed that pedicle screw systems were most appropriate for treatment of spinal instabilities (i.e., trauma, deformity, tumor reconstruction, spondylolisthesis, etc.). In general, the panel was against down-classification of pedicle screw systems in treating a patient population with degenerative disc disease (DDD) because of a lack of data, as well as the lack of clarity surrounding the definition of this disorder. In addition, the reported treatment outcomes for this DDD population also appeared to be device-dependent.

The specific risks identified in relation to pedicle screw fixation at this 1994 panel meeting were:

- Device Related Risks
    - Hardware breakage (including screw breakage)
    - Implant loosening
    - Loss of screw purchase
    - Pedicle fracture
    - Canal or root impingement
    - Dural tears
    - Failure to heal
    - Pseudarthrosis
    - Reoperation

- Operative Risks
    - Poor screw placement
    - Blind application
    - Surgical technique or judgment error
    - Steep learning curve for new users
    - Infection
    - Bleeding/vascular injury
    - Nerve damage

The 1993 and 1994 Classification panel meetings did not discuss use of screws in the cervical spine and also remained silent on screw use in skeletally immature patients (i.e., a subset of pediatric patients, as defined by the FDA).

2.3. 1995 Classification Proposed Rule

On October 4, 1995, the FDA issued a formal call for public comments regarding classification of pedicle screws, specifically on the recommendations of the panel regarding this proposed classification. The panel recommended that the FDA classify into Class II the previously unclassified preamendments pedicle screw spine systems intended for the treatment of severe spondylolisthesis (Grades 3 and 4) at the L5-S1 level. The panel also recommended that the postamendments pedicle screw spinal systems intended for degenerative spondylolisthesis and spinal trauma be reclassified from Class III to Class II. For all other indications, these pedicle screw systems were considered to be postamendments Class III devices, for which a premarket approval (PMA) application was required. The FDA further proposed to expand the intended uses of the device to include pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion in the treatment of acute and chronic instabilities and deformities, including spondylolisthesis, fractures and dislocations, scoliosis, kyphosis, and spinal tumors.

2.4. 1998 Classification Final Rule

On July 27, 1998, after receiving and addressing comments to the 1995 Proposed Rule for classification of pedicle screw systems, thoracolumbosacral pedicle screw systems were classified as Class II devices for the following indications: degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, tumor, and failed previous fusion. DDD was specifically excluded due to a lack of conclusive clinical data and is still considered Class III. In addition, this final rule was silent regarding use of pedicle screws in the cervical spine and in skeletally immature patients.

2.5. 2001 Publication of Technical Amendment

A technical amendment was published in 2001 to correct the omission of one intended use – the use of pedicle screw systems in the treatment of severe spondylolisthesis (Grades 3 and 4) at the L5-S1 level. Additionally, this amendment acknowledged existence of limited prior cervical screw use (e.g., Townley Pedicle Screw Plating System with various uses from C2-S1). Because the use of pedicle screw systems in the cervical spine as well as use in a skeletally immature patient population was not specifically addressed by the Panel in any meeting, classification of these preamendments devices was deferred until these devices were addressed by Panel input.

2.6. 2009 Federal Register Notice and 515(i) Reclassification Petition

Through the April 9, 2009 Federal Register Notice [Docket No. FDA-2009-M-0101], the Agency requested safety and effectiveness information (i.e., 515(i) request for information) on the remaining twenty-five preamendment Class III 510(k) device types, to determine appropriate classification. One of these device types included

pedicle screw systems for use in the thoracic, lumbar, and sacral spine as an adjunct to fusion for treatment of degenerative disc disease and types of spondylolisthesis for which the classification process had not been finalized (i.e., types of spondylolisthesis other than severe spondylolisthesis (Grades 3 or 4) or degenerative spondylolisthesis with objective evidence of neurologic impairment). As part of the docket responses to this 515(i) request for information, data was submitted regarding posterior cervical screw fixation. As this information was not in the scope of the 515(i) request for information, and pedicle screws for the cervical spine are unclassified medical devices, the FDA requested that OSMA submit a separate classification petition. Because pedicle screw use in the cervical spine has not previously been discussed at a classification panel meeting, a panel meeting to discuss classification is required per Section 513(b) of the Act.

2.7. 2011 Petition to Request Classification for Posterior Cervical and Lateral Mass Screws

The subject panel meeting is intended to address the current petition drafted by OSMA to support classification (from unclassified to Class II) of posterior pedicle and lateral mass screws for use in the cervical spine. Please see Appendix A for a full copy of this petition.

With regards to the classification process, the FDA relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective for its stated conditions of use. As defined in 21 CFR 860.7, valid scientific evidence includes evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience.

3. Indications for Use

The indications for use for posterior cervical screw fixation systems, as proposed by the OSMA petition as well as the FDA, are presented below.

3.1. Petition from Orthopedic Surgical Manufacturers Association

"Lateral mass and pedicle screw systems are intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion during bone graft healing and fusion mass development and/or to restore the integrity of the spinal column even in the absence of fusion for a prolonged period for the following acute and chronic instabilities of the cervical spine (C1 to T3 inclusive): trauma, including spinal fractures and/or dislocations; instability or deformity; pseudarthrosis or failed previous fusions; and degenerative disease, including intractable radiculopathy and/or myelopathy, neck and/or arm pain of discogenic origin as confirmed by radiographic studies, and degenerative disease of the facets with instability; and tumors. Spinal screw fixation is achieved with posterior pedicle and lateral mass screws implanted from C1 to T3 levels inclusively."

3.2. FDA Proposed Indications for Use

"Posterior cervical fixation systems utilizing pedicle and lateral mass screws, implanted from the C1 to C7 levels, are intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion for the following acute and chronic instabilities of the cervical spine and craniocervical junction: traumatic spinal fractures and/or traumatic dislocations; instability or deformity; failed previous fusions (e.g., pseudarthrosis); tumors involving the cervical spine; and degenerative disease, including intractable radiculopathy and/or myelopathy, neck and/or arm pain of discogenic origin as confirmed by radiographic studies, and degenerative disease of the facets with instability. These systems are also intended to restore the integrity of the spinal column even in the absence of fusion for a limited time period in patients with advanced stage tumors involving the cervical spine in whom life expectancy is of insufficient duration to permit achievement of fusion."

The FDA's proposed indications for use differ from those presented in the OSMA petition in the following regards:

- Posterior cervical fixation systems were limited to use in the C1 through C7 levels to highlight classification of cervical screws alone.

- The use of these systems in the absence of fusion for a prolonged period was limited to patients with advanced stage tumors involving the cervical spine in whom life expectancy is of insufficient duration to permit achievement of fusion.

Additionally, both FDA's and OSMA's proposed indications for use remain silent on use of cervical pedicle and lateral mass screws in a skeletally mature patient population, which implies that use would be warranted in both the skeletally mature and immature patient populations. It is important to note that other than use in patients with advanced stage tumors, all prescribed indications include cervical screw use as an adjunct to fusion.

The FDA confirmed the safety and effectiveness profile of cervical pedicle and lateral mass screws, as presented in the OSMA petition. However, based on the available clinical evidence, three specific areas requiring additional consideration were identified:

- Use of additional screw trajectories (at the C2 level)

- Use in a pediatric population as an adjunct to fusion

- Use in the absence of fusion for a limited time period

Some of these areas of additional consideration are directly reflected in the FDA's proposed indications for use (i.e., cervical screw use in a pediatric population and use in the absence of fusion for a limited time period) while others are not (i.e., cervical screw use with different screw trajectories). These areas of consideration, along with questions to the panel, are discussed in detail in Section 6.3 of this FDA Executive Summary.

Based on the available clinical evidence, FDA believes that several components of the proposed indications for use, as presented in the OSMA petition, may require some modification for clarity. The panel will be asked to comment on the adequacy of the Petitioner's and FDA's proposed indications for use.

4. Clinical Background

This section summarizes the history as well as the various clinical uses of screws in the cervical spine, as documented in the literature. The cited articles have been provided in Appendix C for reference.

4.1. Evolution of Cervical Screw Use

4.1.1. Lateral Mass Fixation

Posterior cervical screw fixation was first described in the 1970s by Roy-Camille, who reported use of lateral mass screws and plates for treatment of traumatic fractures (Sekhon, 2005). In the 1980s, use of cervical lateral mass screws as the anchor component of posterior plating systems was popularized. This was largely because screw-based systems provided a method to achieve cervical fixation in the presence of compromised or deficient posterior spinal column elements where existing wiring techniques were inadequate (Liu JK, 2001; Roy-Camille, 1992; Cooper, 1988). Soon after, lateral mass screw-rod systems were introduced and permitted placement of cervical screw anchors independent from the constraints imposed by plate systems (e.g., such constraints included fixed distances between screw holes in the plate). The versatility provided by modular screw-rod systems permitted extension of surgical indications for cervical screw-based constructs to include post-laminectomy stabilization, failed prior fusions, tumors, complex spinal instabilities, and spinal deformities (Liu JK, 2001; Horgan, 1999).

4.1.2. Pedicle Fixation

The use of pedicle screw fixation in the cervical spine was initially introduced as a method for promoting direct healing of bone; for example, in the case of a C2 Hangman's fracture, as described by Leconte in the 1960s (ElMiligui, 2010). Cervical pedicle fixation, in combination with screw-plate and screw-rod systems, was subsequently introduced for use primarily at the C2 and C7 spinal levels. At C2, medially-directed screw placement into the pedicle is preferable since laterally directed screw placement endangers the vertebral artery at this spinal level. At C7, local anatomy favors the placement of pedicle screws over lateral mass screws. In the majority of patients, the vertebral artery enters the foramen transversarium of C6 and is not at risk with C7 pedicle screw placement. Also, the smaller dimensions of the lateral mass, in comparison to lateral mass dimensions at proximal spinal levels, may lead to suboptimal fixation and increase the risk of direct nerve root injury due to screw-nerve impingement by excessively long screws. These limitations are addressed by placement of pedicle screws at the C7 level.

Currently, pedicle screw use at the C3-C6 spinal levels is not widely practiced in the United States due to concerns regarding the potential for neurovascular injury, technical challenges associated with placement of these screws, and the adequacy of lateral mass fixation for the most commonly treated spinal conditions. However, United States (US) surgeons acknowledge that pedicle fixation may provide the only feasible fixation site in conditions where the lateral masses are deficient (e.g., hypoplastic or deformed lateral masses and lateral mass destruction secondary to tumor). Despite the technical challenges associated with placement of C3-C6 pedicle screws, studies have demonstrated safe and effective use of pedicle screws in the C3-C6 spinal levels for treatment of traumatic instability (Abumi, 1994) as well as non-traumatic instability (Abumi, 1997).

4.1.3. Atlantoaxial (C1-C2) Spinal Instrumentation

The biomechanical limitations associated with wire-based techniques at the C1-C2 levels led to the introduction of the transarticular screw technique by Magerl in the 1980s (Harms, 2001). As initially described, this technique places a single screw across the C1-C2 articulation bilaterally. Limitations associated with the Magerl technique include the inherent risk of vertebral artery damage and the inability to utilize this technique bilaterally in up to 20% of patients due to regional anatomic variation (Sasso, 2007; Madawi, 1997). This stimulated the development of alternate techniques. Subsequently, the introduction of a C1-C2 screw-rod construct provided a screw-based method utilizing independent screw anchors in the C1 and C2 vertebra to provide posterior fixation at these anatomically unique levels (Harms, 2001).

4.2. Current Standard of Care

The evidence provided in the petition documents the evolution of the standard of care for cervical posterior stabilization and fusion from the use of non-rigid bone anchors (e.g., wires, cables), with or without longitudinal rods, to the use of screw-rod constructs that achieve rigid fixation by attachment to the posterior osseous elements of the cervical spine. The versatility and success of cervical screw-rod constructs has been documented in medical literature for treatment at all cervical levels (C1-C7) as well as for the extension of spinal instrumentation constructs proximally to include the occiput and distally to the thoracic spine. Treatment success has been documented for a wide spectrum of cervical disorders including traumatic fractures and dislocations, failed prior fusions, tumors, specific cervical degenerative disorders, post-laminectomy stabilization, complex spinal instabilities, and spinal deformities.

With respect to the effectiveness of posterior cervical screw-rod constructs, current literature shows that cervical fusion is consistently achieved at higher rates with the use of posterior screw fixation, compared to the fusion rates reported with the use of alternative fixation methods, such as cables, hooks, and wiring (Stock, 2006). The favorable performance of screw fixation systems compared to cables, hooks, and wiring systems in promoting fusion is attributed to the greater rotational and

extension stability provided by screws. Furthermore, screw fixation systems are not dependent on the presence of intact posterior elements, such as the spinous processes or laminae (Xu, 1999; Anderson, 1991), which permits use of screws for conditions where wire-based constructs are ineffective.

With respect to the safety of posterior cervical screw-rod constructs, the reported rates of neurologic events and reoperations is lower in patients treated with posterior cervical lateral mass and pedicle screws compared to treatment using cables, hooks, and wiring. In addition, cervical screw placement accuracy rates are high and are similar to the accuracy rates reported in the literature for thoracic and lumbar pedicle screws (Kosmopoulos, 2007). In conclusion, there exists sufficient evidence to support cervical screw use as the current standard of care when direct and rigid immobilization of the posterior elements is necessary to stabilize the cervical spine at a given level or levels.

4.2.1. Subaxial (C3-C6) Cervical Instrumentation (Lateral Mass and Pedicle Fixation)

4.2.1.1. Lateral Mass Screw Use in Cervical Spine

When treating the subaxial cervical spine (C3-C6) levels, lateral mass screws are predominantly used as anchor points for cervical screw-rod fixation systems. Various lateral mass screw trajectories have been described by Magerl, Anderson, and An (Jeanneret, 1991; Anderson, 1991; An, 1991). The basic principle common to current techniques is direction of the screw from the center of the lateral mass in a cephalad and lateral direction to obliquely span the lateral mass and direct the screw tip toward the upper, outer portion of the lateral mass, away from the nerve root, spinal cord, and vertebral artery. Recently, large case series have been presented to support the safety and effectiveness of lateral mass screws as the bone anchor for cervical screw-rod fixation systems (Katonis, 2011; Deen, 2006; Sekhon, 2005). Analysis of these combined series (468 patients, 3576 screws) show no spinal cord injuries and no vertebral artery injuries related to the use of lateral mass screws. Complication rates were also low: radiculopathy (0.7 – 4%, not necessarily screw-related), screw-breakage (0.22 – 2.8%), rod breakage (0 – 1%), and screw loosening/pull-out (0 – 6%). Finally, fusion success rates across studies were high with screw-rod fixation systems (≥ 97%).

4.2.1.2. Pedicle Screw Use in Cervical Spine

In the US, cervical pedicle screw anchors are most frequently utilized with screw-rod systems when fixation is required at the C2 and C7 spinal levels. At C2, medially-directed screw placement (i.e., pedicular) is necessary as laterally directed screw placement endangers the vertebral artery at the C2 spinal segment. At C7, although lateral mass fixation may be achieved using a modified screw trajectory (Sekhon, 2005), the smaller dimension of the C7 lateral mass, in comparison to lateral mass dimensions at more proximal spinal levels, may lead to suboptimal fixation and is associated with increased risk of

C8 nerve root injury. Successful C7 pedicle screw insertion directed by either direct visualization (Albert, 1998) or fluoroscopic guidance (Yukawa, 2009; Kim, 2007) has been documented without serious neurologic or vascular sequellae.

In the US, screw placement through the pedicles at the C3-C6 levels has not gained universal acceptance due to the availability of lateral mass screws and the perceived risks and technical challenges related to C3-C6 pedicle screw insertion (Ludwig, 1999; Albert, 1998). Several studies document that pedicle screws may be carefully used at the C3-C6 levels (Abumi, 2012; Abumi, 1997; Abumi, 1994), but the majority of these cases are described in an outside the US (OUS) patient population. Cervical pedicle screw perforation rates have been analyzed by level of insertion and by disease process (Uehara, 2010). In a study of 53 patients, with a mean age 64.9 years, there were no clinically important complications, including vertebral arterial injury, spinal cord injury, or nerve root injury caused by any screw perforation. Major perforation rate by vertebral level were as follows: C2 (2/30; 6.7%), C3 (4/49; 8.2%), C4 (6/43; 14.0%), C5 (1/32; 3.1%), C6 (1/41; 2.4%), and C7 (1/45; 2.2%). These rates demonstrate feasibility of using pedicle screws in the subaxial spine. Additionally, major perforation rates by disease process for pedicle screws inserted from C3 to C7 were also analyzed. Perforation rates by disease processes were: spine tumor (0/24; 0%), rheumatoid arthritis (2/59; 3.4%), destructive spondyloarthritis (3/65; 4.6%), athetoid cerebral palsy (2/20; 10.0%), and cervical spondylotic myelopathy (6/40; 15.0%), showing that cervical pedicle screws can be used to treat a variety of different indications. Despite this information, pedicle screw use at the C3-C6 levels is not widely performed in the US at this time, except for situations where lateral mass screw fixation techniques are not applicable.

4.2.2. Atlantoaxial (C1-C2) Spinal Instrumentation

Posterior instrumentation for use in the upper cervical region has evolved from wire fixation supplemented with external mobilization to placement of a single screw across the C1-C2 articulation bilaterally and subsequently to screw-rod techniques that rely on independent placement of screws at the C1 and C2 levels. Stand-alone wiring techniques for C1-C2 fixation have fallen into disfavor due to high pseudarthrosis rates and their inability to provide rigid fixation (Bransford, 2011). A major advance was the introduction of the transarticular screw technique by Magerl in the 1980s, which placed a single screw across the C1-C2 articulation bilaterally. Limitations associated with this technique became evident, including the inherent risk of vertebral artery damage and the inability to utilize this technique bilaterally in up to 20% of patients due to regional anatomic variation (Sasso, 2007; Madawi, 1997). Goel and Laheri (Goel, 1994) described the use of plates in combination with C1 lateral mass screws and C2 pedicle screws.

Subsequently, Harms and colleagues popularized the combination of C1 lateral mass and C2 pedicle screws as part of a screw-rod construct for stabilization of

the C1-C2 segment (Harms, 2001). Use of C2 pedicle fixation provided a partial solution to the difficulties associated with obtaining the required screw orientation, which had been challenging when using the C1-C2 transarticular screw technique. However, the risk of vertebral artery injury due to anatomical variation in its location at the C2 level remained (Bransford, 2011). This led to the development of alternate screw trajectories including the use of C2 translaminar screw placement (Wright, 2004) to reduce the risk of vertebral artery injury.

A second alternative screw trajectory was described for C2 fixation using the C2 pars screw, which utilized a shorter screw length than alternative techniques, thereby permitting the screw tip to stop proximal to the vertebral artery foramen. In the largest reported series in the literature regarding C2 fixation, 339 pedicle screws, 154 C2 transarticular screws, 63 C2 translaminar, and 77 C2 pars screws were inserted with no neurologic injuries reported secondary to screws (Bransford, 2011). In this series, two C2 pedicle screws (0.3%) were associated with anatomic injury to the vertebral artery. One patient was asymptomatic and the second patient died secondary to multiple severe injuries, but did not manifest evidence of stroke. Overall, there was a 1% incidence of unacceptable screw placement across all screw types. As noted by the authors of this study, there was a trend over the past decade to utilize independent C1 and C2 screws rather than transarticular screws. Alternative C2 screw techniques including translaminar and pars placement were considered based on anatomic factors and surgeon preference.

5. Literature Review on Cervical Pedicle and Lateral Mass Screw Fixation – OSMA Analysis

A comprehensive literature review was presented in the OSMA petition regarding the use of pedicle and lateral mass screw fixation in the cervical spine. A PubMed search was conducted on relevant literature articles pertaining to clinical use of these screws published in the last 10 years. Of note, other types of screws were excluded from this analysis, including transarticular, pars, and laminar screws.

In addition, a separate PubMed search was conducted on the use of other cervical fixation methods that included the clinical use of cervical cables, hooks, and/or wiring methods. This search was also conducted on relevant literature articles from the past 10 years. For reference, a summary of the literature review and analysis were provided in Attachments C and D of the OSMA petition (provided in Appendix A).

6. Literature Review on Posterior Cervical Screw Fixation – FDA Analysis

In addition to the extensive literature review conducted and presented in the petition from OSMA, FDA conducted a supplementary literature review to confirm the safety and

effectiveness profile of posterior cervical screw fixation by analyzing the existing clinical literature from 1999 to the present. While this did exclude some pre-1999 references, the FDA also believed a search covering an approximately 10-year span would capture the most relevant research on contemporary cervical screw use, as part of a screw-rod construct. We sought to address the following questions:

1. What is the evidence for safety of screw use in the posterior cervical spine?
2. What is the evidence for effectiveness of posterior cervical screw fixation for the indicated population, as described above?
3. What are the reported adverse events associated with the use of posterior cervical screw spine fixation?

6.1. Methods

On July 6, 2012, we searched two electronic databases (MEDLINE and Embase) using the following terms, which were identical to those identified in the OSMA petition, and also used as a confirmatory measure: ["cervical vertebrae" AND "pedicle" AND "arthrodesis" OR "fusion" OR "screw" OR "bone screw"].

All studies published in English from January 1, 1999 to July 6, 2012 were included. The initial search of the above electronic databases yielded 518 citations after duplicate articles were removed. Of these, a total of 458 citations were presented in English. Different variations of these key terms were also included to expand the results. Further, supplementary searches were conducted of specialty journals, such as Spine, Spine Journal, European Spine Journal, and Journal of Neurosurgery.

An additional search was also conducted to find relevant articles demonstrating use of cervical screw fixation in a pediatric population, as defined by the FDA (≤21 years of age). The search terms included: ["cervical vertebrae" AND "pedicle" AND "arthrodesis" OR "fusion" OR "fixation" OR "instrumentation", "screw" OR "bone screw" AND "pediatric" OR "infants" OR "toddler" OR "child/children" OR "adolescent" OR "teen" OR "girl" OR "boy"].

All studies published in English from January 1, 1999 to July 6, 2012 were included. The initial search of the above electronic databases yielded 138 citations after duplicate articles were removed. Of these, a total of 123 citations were presented in English. Different variations of these key terms were also included to expand the results. Further, supplementary searches were conducted of specialty journals, such as Spine, Spine Journal, European Spine Journal, Journal of Neurosurgery, and Journal of Pediatric Orthopedics.

6.2. Results

The results of our literature review generally corresponded to the conclusions reached in the OSMA petition where cervical pedicle and lateral mass screws are used in fusion procedures. Due to the extension of the time parameters of the FDA literature review, several additional articles were available for analysis. These included several articles on atlantoaxial (C1-C2) screw fixation (Bransford, 2011; Dorward, 2011), as

well as the use of screws in the subaxial (C3-C7) spine (Kotil, 2012; Nakashima, 2012). A recent study also examined the failure rate of cervical screw-rod systems that used cannulated or multi-axial pedicle screws, and found that the reported 4.2% failure rate was similar to that reported for both posterior cervical and lumbar spinal fusions (Okamoto, 2012).

Additionally, the FDA identified specific areas requiring further consideration that were not discussed in detail in the OSMA petition. These areas include the use of cervical screws in (1) additional screw trajectories, (2) a pediatric population, and (3) for a prolonged period in the absence of fusion. Additional screw trajectories have been the subject of a good proportion of the currently available literature and are discussed above in Section 4 (Clinical Background), as well as in Section 6.3.1 below. In contrast, the use of posterior cervical screw fixation in the absence of fusion is not currently well documented (see Section 6.3.3). Finally, the supplementary pediatric literature review performed by the FDA yielded over 70 articles that also included data on an adult patient population. After excluding articles that were not exclusively studying a pediatric population (i.e., patients $\leq$ 21 years of age), not specific to cervical screw use, and single case study reports, the remaining 23 total references were reviewed to ascertain both the non-clinical and clinical evidence regarding the safety and effectiveness of cervical screw use in a pediatric population. A summary of the cervical screw use in a pediatric population is presented below in Section 6.3.2.

6.3. Additional Considerations

In our examination of the literature, several specific uses of these devices were noted. A discussion of these uses is included below.

6.3.1. Additional Screw Trajectories

Also discussed above in Section 4 (Clinical Background), as surgeons' recognition of the unique anatomical features of the C2 vertebra has received increased attention in the medical literature, the terms used to describe screw fixation in the region of the pedicle and lateral mass of the C2 vertebra have evolved. Specifically, C2 pedicle fixation is generally described as screw purchase in the portion of C2 connecting the posterior osseous elements with the vertebral body (i.e., fixation in the region beneath the superior facet and anteromedial to the transverse foramen) (Sasso, 2007). This type of fixation has been distinguished from screw fixation in the pars interarticularis, or the region of the C2 vertebra between the superior and inferior articular processes. In addition, use of transarticular screws (across the C1-C2 level) has continued to be described as an alternative anchor for rod-screw constructs that span the C1-C2 levels. More recently, a translaminar screw trajectory (exclusively at the C2 level) has been described as a screw anchor site for use when C2 pedicle screws are not possible due to aberrant anatomy or when a "safer" screw trajectory is desired.

FDA believes that the use of other screws, such as the transarticular screw (across the C1-C2 level), pars screw (limited to the C2 level), and translaminar screw (limited to the C2 level), are safe and effective at the specific level(s) indicated for use in patients whose osseous structure is dimensionally adequate to accommodate screw fixation, as determined by appropriate cross-sectional radiographic imaging studies. The panel will be asked to discuss inclusion of the specific screw trajectories and screw types noted above for use in posterior cervical screw fixation systems.

6.3.2. Posterior Cervical Screw Fixation Use in Pediatric Population

The FDA considers pediatric medical devices as those devices intended to treat or diagnose diseases or conditions from birth through age 21. In addition, the Agency further defines pediatric patients as noted below in Table 1.

Table 1. FDA Definitions of Pediatric Population Subgroups

Description	Age
Neonate / Newborn	From birth to 1 month of age
Infant	Greater than 1 month to 2 years of age
Child	Greater than 2 to 12 years of age
Adolescent	Greater than 12 to 21 years of age
All pediatric patients (≤ 21 years)	

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm

While the FDA considers the pediatric patient (≤ 21 years) to be a vulnerable population, it is important to note that it is current standard of care to use cervical screw fixation techniques when a patient's osseous structure is dimensionally adequate to accommodate screw placement. As such, in the limited instances in which posterior stabilization is needed, this may include subjects that are currently classified by the Agency as pediatric (≤ 21 years) patients.

It is important to note that half of the key studies identified in the OSMA petition also included some pediatric subjects, as defined by the Agency (Abumi, 2000; Alosh, 2010; Arnold, 2005; Aryan, 2008; Goel, 2002; Harms, 2001; Hasegawa, 2008; Ishikawa, 2010; Ito, 2008; Jian, 2010; Kim SH, 2007; Lee SH, 2010; Lee GY, 2007; Li, 2008; Liu Y, 2009; Ogihara, 2010; Ondra, 2006; Sairyo, 2009; Sciubba, 2009; Wang, 2011; Yoshimoto, 2009; Yukawa, 2009). Additionally, several large studies not cited in the petition, but subsequently reviewed by the FDA, have also included patients less than 21 years of age. For example, a large analysis of 1,026 screws in 143 patients,

some as young as 12 years old, documented the safe and effective use of lateral mass screw fixation between the C3 and C7 levels in both pediatric and adult populations (Sekhon, 2005). These articles provide evidence supporting the safe and effective use of posterior cervical screw fixation in patients who are defined as pediatric. However, because the data are not stratified per age, an in-depth analysis cannot be completed on the pediatric cohorts contained in these studies.

A subset of the literature reviewed by the FDA has exclusively examined cervical screw use in a pediatric population. There is supportive evidence documenting the anatomic feasibility of specific screw trajectories in the cervical spine in specific pediatric patient subgroups (Chern, 2009; Cristante, 2012; Ferri-de-Barros, 2010; Kanna, 2011). As briefly summarized in Table 2 below, there exists some controversy regarding the feasibility and potential safety of specific posterior cervical screw trajectories in these subgroups (Vara 2006; Brockmeyer, 2000). However, the majority of these anatomic studies show that while there exists variability in anatomic structures according to age, careful preliminary radiographic assessment can allow successful posterior cervical screw placement in patients as young as 1 or 2 years of age.

Table 2. Radiographic and Cadaveric Studies Providing Data Regarding Feasibility of Cervical Screw Placement in the Pediatric Patient Population

Investigator (Year)	Number of Subjects	Age Range	Screw Sites Analyzed	Results
Chamoun (2009)	76	1.5-16 years	C1 lateral mass	Retrospective review of CT scans to assess ability of C1 lateral masses to accommodate screw fixation. Only one of 152 lateral masses (in a 19- month old subject) had a width < 4mm (unable to accommodate a 3.5mm diameter screw).
Chern (2009)	69	1.5-16 years	Translaminar (C2-C7 levels)	Retrospective review of CT scans to compile an anatomic description establishing useful guidelines for axial and subaxial translaminar screw placement in a general pediatric population. 30.4% of patients between the ages of 1.5-16 years could accept bilateral translaminar screws at C2 while subaxial (C3-C7) could rarely be placed.
Cristante (2012)	75	2-10 years	C2 screws: intralaminar, pedicle, lateral mass (pars)	Retrospective review of CT scans to demonstrate feasibility of using 3.5-mm screws at the C2 level in children. Pedicle and laminar screw placement was feasible in the majority of 2-10 year old patients. Length of lateral mass (9mm) was considered an adverse factor which did not support use of lateral mass placement.
Ferri-de-Barros (2010)	23	2-11 years	C1 lateral mass, C2 laminar and pedicles	Retrospective review of CT scans to assess feasibility of screw use in pediatric patients. 24% of C2 pedicles, 65% C2 laminae, and 95% C1 lateral masses were deemed acceptable for 3.5mm screw use.
Kanna (2011)	30	1-14 years	C1 lateral mass, C2-C7 pedicles	Prospective review of CT scans to assess anatomic feasibility of C2-C7 pedicle and C1 lateral mass screw placement in three groups of pediatric patients (Group A: <5 yrs.; Group B: 5-10yrs.; Group C: >10 years). Osseous

Investigator (Year)	Number of Subjects	Age Range	Screw Sites Analyzed	Results
				dimensions do not restrict pedicle or C1 lateral mass screw placement except at the C3 level in most subjects. At least 75% of adult pedicle width is achieved by age 5.
Vara (2006)	47	3-18 years	C3-C7 pedicles	Cadaveric spine study showing that pedicle screws may not be safe at all levels in all pediatric patients, particularly in younger patients. The anteroposterior (AP) spinal canal diameter is similar to that of an adult by 3-5 years of age.
Brockmeyer (2000)	31	4-16 years	C1-C2 transarticular (TA)	Prospective CT evaluation was performed to determine feasibility of TA screw insertion. 94% of patients had adequate osseous dimensions to permit placement of at least one TA screw. 9.7% of subjects were determined to have unsuitable anatomy for placement of TA screws bilaterally.

In addition to the above anatomic studies, there exists documented clinical experience demonstrating the safe and effective use of posterior cervical screws in patients under the age of 21 years. A recent prospective study included an analysis of the feasibility, safety, and efficacy of cervical pedicle screw use in a pediatric population, ranging in ages from 3-13 years (Rajasekaran, 2012). Use of transarticular screws (C1-C2) has been documented for treatment of 67 pediatric patients ranging in age from 1.7 years to 16 years (Gluf, 2005). An additional study (Reilly, 2006) demonstrated safe use of transarticular screws in patients as young as 5 years of age. Screw fixation in the lateral masses of patients ranging from 3 to 16 years has also been documented and is considered to be current standard of care (Hedequist, 2010 and 2008). The lower age bound for successful placement of various types of posterior cervical screws noted in the current literature is summarized in Table 3.

Table 3. Pediatric Posterior Cervical Screw Fixation - Lowest Reported Age According to Anchor Site and Spinal Level

Spinal Level	Site	Lowest Reported Age	Screw Size	Investigator (Year)
C1	Lateral Mass	3 years	3.5mm	Jea (2007)
C2	Pars	1.3 years	3.5mm	Anderson RC (2007)
	Pedicle	3 years	3.0mm	Rajasekaran (2010)
	Translaminar	3 years	4.0mm	Leonard (2006)
C1-C2	Transarticular	1.3 years	2.5mm	Gluf (2005)
C3-C7	Lateral Mass	3 years	3.5mm	Hedequist (2010)
C3-C7	Pedicle	6 years	3.0mm	Rajasekaran (2010)

The studies that report clinical data regarding posterior cervical screw use in the pediatric population are summarized below in Table 4. The majority of the reported clinical experience relates to screw use at the atlantoaxial (C1-C2) levels, with additional documented use of lateral mass screws in the subaxial (C3-C7) spine (shaded boxes in Table 4). One study did present successful use of cervical pedicle screws in patients 3-13 years old (Rajasekaran, 2012). Taken together, over 650 posterior cervical screws have been used at the C1-C2 levels in patients ranging from 1.3 to 17 years of age. Additionally, more than 180 cervical screws have been used in the subaxial spine for this pediatric patient population. The information contained in the literature, which focuses exclusively on posterior cervical screw use in a pediatric population, is limited compared to the adult population. However, combined with the documented use in larger studies that also include adult patients, there is a large and growing body of evidence that documents the safe and effective use of posterior cervical screws in patients less than or equal to 21 years of age. A data abstraction table for key studies presenting the safety and effectiveness of cervical screw use in a pediatric population has been included in Appendix B.

Table 4. Summary of Studies Reporting Clinical Data Regarding Posterior Cervical Screw Use in the Pediatric Population

Investigator (Year)	Number of Cases	Age Range	Screws Utilized	Number Implanted	Results
Anderson (2007)	25	1.3-17 years	C1-C2 Transarticular	15	C1 lateral mass, C2 pars, C2 translaminar, and subaxial lateral mass screws were used when transarticular screws were not feasible. All patients who reached 3-month follow-up achieved fusion (22)
			C1 Lateral mass	11	
			C2 Pars	24	
			C-2 Translaminar	1	
			Subaxial Lateral mass	6	
	70	Not specified	C1-C2 Transarticular	140	Not specified
Brockmeyer (1995)	10	6-16 years	C1-C2 Transarticular (8 cases); Subaxial lateral mass plates/screws (2 cases)	16 Transarticular; 4 lateral mass plates (# of screws not specified)	No instrumentation failures, neurologic status maintained or improved
Brockmeyer (2000)	29	4-16 years	C1-C2 Transarticular	55	No vertebral artery (VA) or neural injuries
Chamoun (2009)	7	1.6-14 years	C2 Translaminar	8	100% Fusion; Postoperative complication of dysphagia attributed to excessively long C1 screw
			C2 Pars	3	
			C3 Translaminar	1	
			Upper thoracic translaminar (T1, 3, 5)	6 (2 at each level)	
			Other C1 Lateral mass and Occiput screws used, but not specified		

Investigator (Year)	Number of Cases	Age Range	Screws Utilized	Number Implanted	Results
Desai (2010)	8	5-13 years	C1 Lateral mass	16	100% Fusion; C3 lateral mass screws used when C2 anatomy not suitable for screw placement
			C2 Pedicle	12	
			C3 Lateral mass	4	
Gluf (2005)	67	1.7-16 years	C1-C2 Transarticular	127	100% Fusion; 2 VA injuries which did not result in neurologic sequellae
Haque (2009)	17	3-17 years	C1 Lateral mass	26	100% Fusion; No VA injuries or implant-related complications
			C2 Pars	28	
			C2 Laminar	4	
			C3 Lateral mass	8	
Hedequist (2008)	25	6-15 years	A total of 112 screws were placed in the anterior and posterior cervical spine (17 posterior-only procedures, 7 anterior/posterior procedures, and 1 anterior-only procedure).		100% Fusion
Hedequist (2009)	17	3-16 years	C2 Transarticular	7 patients	100% Fusion; One reoperation for excessively long C1-C2 transarticular screw
			C2 Pars	9 patients	
			C2 Translaminar	1 patient	
Hedequist (2010+)	31	3-16 years	Lateral mass (C3-C7); C2 Pars	141	No screw-related complications
Heuer (2009)	6	7-17 years	C1 Lateral mass	12	100% Fusion
			C2 Pedicle	10	
			C2 Translaminar	2	
Jea (2007)	4	2-8 years	C1 Lateral mass	8	100% Fusion; One VA injury due to C1 lateral mass screw without reported neurologic sequellae
			C2 Pars	7	
			C2 Translaminar	1	
Karandikar (2012)	31	2-17 years	C1-C2 Transarticular; Additional subaxial lateral mass and occipital screws were placed, but specifics were not described	47	94% Fusion rate; 18 out of 47 transarticular screws were suboptimally placed; One broken transarticular screw was noted; Non-traditional implants were utilized including non-spinal plates and small screw sizes (2.4mm and 2.7mm)

Investigator (Year)	Number of Cases	Age Range	Screws Utilized	Number Implanted	Results
Leonard (2006)	3	3-16 years	C1 Lateral mass	4	No VA or neurologic injuries
			C2 Translaminar	6	
Rajasekaran (2012)	16	3-13 years	Pedicle	51	No screw-related complications
			Subaxial pedicle	24 (of 51)	
Reilly (2006)	12	5.8-16.9 years	C1-C2 Transarticular	23	100% Fusion; In 2 cases, transarticular screws were used in conjunction with longitudinal rods for multilevel fusions.
Tauchi (2012)	5 screw-rod cases in 11 total patients	4-13 years	C1-C2 Transarticular	4	Five of 11 total cases involved screw-rod constructs; Other constructs included rod-wire (4) and transarticular constructs (2); Screw-related problems included C1 arch fracture (1 case) and C2 pedicle fracture (1 case).
			C1 Lateral mass	8	
			C2 Pedicle	8	

NOTE: Studies that include transarticular C1-C2 screw are included. Transarticular screw use without concurrent use of longitudinal members is outside the scope of this panel deliberation. However, since transarticular screws may also be utilized in cervical instrumentation constructs as a cervical anchor in conjunction with use of longitudinal members, the available clinical data regarding use of such screws in the pediatric population is considered relevant and is included for completeness.

The proposed Indications for Use submitted by FDA and OSMA is silent regarding patient age, as the language regarding use of posterior cervical screw fixation in skeletally mature subjects has been removed for the purposes of this classification petition. The FDA recognizes that it is current standard of care to use cervical screw fixation techniques when a patient's osseous structure is dimensionally adequate to accommodate screw placement. As such, this may include subjects that are currently classified by the Agency as pediatric (≤ 21 years) patients. It is important to note that the Agency does not only consider the patient's age when including this special patient population, but more so the presence of adequate bone structure to accommodate screws in the posterior cervical spine.

The panel will be asked to discuss the adequacy of the documented literature in support of inclusion of a pediatric population (≤ 21 years) for treatment with posterior cervical screw fixation systems. This discussion is under the assumption that a given patient's osseous structures are adequate to accommodate screw fixation in the posterior cervical spine for fusion procedures.

6.3.3. Posterior Cervical Screw Fixation Use for a Prolonged Period in the Absence of Fusion

The proposed indications for use contained in the OSMA petition include a statement that cervical screw systems are intended "to restore the integrity of the spinal column even in the absence of fusion for a prolonged period". This statement differs from the intended use of thoracic and lumbar screw fixation (21 CFR 888.3070), which states that these devices are intended "to provide immobilization and stabilization of spinal segments in skeletally mature patients as an adjunct to fusion". Contained in the OSMA petition is a case series describing successful use of posterior cervical lateral mass and pedicle screw fixation systems for stabilization of spinal segments in subjects with advanced stage spinal tumors in whom life expectancy is not of sufficient duration to permit achievement of fusion. In these patients, posterior instrumentation is a necessity in stabilizing the OCT junction.

While surgical intervention is not always recommended, it is considered in these main scenarios: (1) spinal instability or deformity, (2) progressive neurologic deficit, (3) substantial spinal cord compression, and (4) intractable neck pain that is unresponsive to non-operative treatment (Oda, 2006). Oda and colleagues studied a total of 32 patients with significant metastases, who were treated with a cervical screw-rod system. Clinical outcomes demonstrated restoration and maintenance of spinal stability in 94% of the patients through the survival period. Of note, 3 patients died before fusion was established. The authors concluded that the use of cervical pedicle screw fixation provided spinal stability, pain relief, and neurologic function to patients with metastases (Oda, 2006). The investigators did not use bone graft in 27 cases (52%) in patients with life expectancy less than two years and noted only one case of screw loosening in this subgroup. However, the investigators note that determination of life expectancy is difficult and requires careful consideration of the nature of the primary tumor. In the Agency's proposed Indications for Use Statement, an attempt is made to clarify this issue by inclusion of language stating, "These systems are also intended to restore the integrity of the spinal column even in the absence of fusion for a limited time period in patients with advanced stage tumors involving the cervical spine in whom life expectancy is of insufficient duration to permit achievement of fusion."

FDA believes that cervical pedicle screw systems may be used to restore the integrity of the spinal column even in the absence of fusion for a prolonged period in the case of patients with advanced stage tumors. The panel will be asked to comment on the treatment of patients with posterior cervical screw fixation techniques (limited to tumor), in whom a fusion would not be expected.

7. Risks to Health

7.1. Overview of the Published Literature

Based on a review of the published literature and the petitioner's review of FDA's Manufacturer and User Facility Device Experience (MAUDE) database, the following risks to health were identified in the OSMA petition for lateral mass and pedicle screws used in the cervical spine:

- Malposition
- Implant loosening
- Device breakage
- Disassembly
- Malfunction – Device
- Bone fracture
- Graft settling/Displacement
- Loss of correction
- Pseudarthrosis
- Bleeding/Vascular injury
- Neurologic injury
- CSF leak
- Wound
- Infection
- Skin irritation
- Cardiac
- Respiratory
- Revision surgery
- Death

Of note, these risks to health are similar to those associated with spinal instrumentation surgery.

7.2. Unique Risks to Health

There are several notable anatomic features of the cervical spine, including the presence of typical (C3-C6) and atypical (C1, C2 and C7) vertebra, as well as unique vasculature, such as the vertebral arteries. As such, there is the potential for unique risks to health in the cervical spine, particularly associated with vascular injury (i.e., vertebral artery injury). However, in a recent survey of more than 5,600 cervical spine surgery operations, the overall incidence of vertebral artery injury was 0.14% (or 8 cases out of 5,641 surgeries), which was less than the incidence of vascular injury in anterior cervical decompression procedures, which was reported to be 0.18% (Neo, 2008).

Other than the risks associated with the presence of the vertebral arteries, the panel will be asked to discuss other unique risks that may be present in the cervical spine.

7.3. Adverse Events Associated with Posterior Cervical Screw Fixation

While adverse events are not consistently reported in the literature, the safety profile of cervical screw fixation systems is considered to be fairly established. As the petition outlines (Table 7, Pages 24 and 111), the reported adverse events demonstrate fairly low rates of events, as well as the absence of a single major risk.

A MAUDE database search was conducted by OSMA related to adverse events reported for various product codes (for Class II devices). In an effort to obtain supplementary information, the Agency conducted a MAUDE search for reported adverse events for cervical screw use, outside the bounds of the assigned product codes, given the nature of off-label use of these systems. First, our search did not find any recalls associated with the single cleared system for which cervical screw use is included (Medtronic Axis Fixation System, K062254). Second, the 29 reported adverse events (reported through July 5, 2012) consisted of 3 deaths, unrelated to the device, 11 malfunctions, and 15 injuries. Review of the reports revealed events such as screw stripping during surgery, screw fracture, set screw stripping during implantation, rod breakage, screw disassembly, malpositioned screw, screw back-out, screw loosening, connector disassembly, and plate fracture.

FDA has identified several potential risks to health associated with posterior cervical screw fixation, based on reviews of the available literature and currently reported adverse events. These risks are generally in agreement with the list presented in the OSMA petition.

A reasonable assurance of safety is defined in 21 CFR 860.7(d)(1) as the probable benefits to health from use of the device outweighing any probable risks for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use. The regulation also states that the evidence shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use. The panel will be asked whether the evidence demonstrates a reasonable assurance of safety for the indications for use described above.

7.4. Effectiveness of Posterior Cervical Screw Fixation

As described by the literature review provided in the OSMA petition, as well as the supplementary literature references provided in this FDA Executive Summary, there appears to be consistent evidence that posterior cervical screw fixation is an effective method of providing stability to the cervical spine for a variety of different indications. Fusion success rates were noted to be in the range of 93-100% in the OSMA petition, which included a literature analysis of primarily skeletally mature patients treated with cervical pedicle and lateral mass screws. The petition also presented 11 studies showing a maintenance or improvement of neurologic outcomes and 5 studies showing a pain and/or disability improvement. Further, FDA analysis of more recent literature also confirmed these high fusion success rates with some large studies showing high fusion rates ($\geq$ 97%) with screw-rod fixation systems using cervical lateral mass screws. Literature exclusively reporting on posterior

cervical screw use in a pediatric population also presented fusion success rates in excess of 94% in this patient population.

A reasonable assurance of effectiveness is defined in 21 CFR 860.7(e)(1) as clinically significant results in a significant portion of the target population, when used for these indications for use and conditions of use when accompanied by adequate directions for use and warnings against unsafe use. The panel will be asked whether there is a reasonable assurance of effectiveness for posterior cervical screw systems for the indications for use described above.

8. Special Controls

8.1. Overview of Device Classification

The FDA uses a 3-tiered classification system for medical devices. A device is classified based on the levels of risk and controls needed to provide a reasonable assurance of safety and effectiveness. The following descriptions provide more detail on each class of devices, as determined by the FDA:

8.1.1. Class I Devices (21 CFR 860.3(c)(1))

- Low risk devices.
- Devices classified as Class I are subject only to the general controls, which include provisions regarding adulteration, misbranding, device registration and listing, premarket notification, banned devices, notification, records and reports, restricted devices, and good manufacturing practices (GMPs).
- Class I devices generally are exempt from requiring submission of a premarket notification 510(k).

8.1.2. Class II Devices (21 CFR 860.3(c)(2))

- Moderate risk devices.
- Devices are classified as Class II if general controls alone are insufficient to provide reasonable assurance of safety and effectiveness. Additionally, there must be sufficient information to establish special controls for these devices, which may include performance standards, performance data requirements (non-clinical and/or clinical), labeling requirements, postmarket surveillance, patient registries, development and dissemination of guidance documents, and recommendations.
- Class II devices generally require submission of a premarket notification 510(k).

8.1.3. Class III Devices (21 CFR 860.3(c)(3))

- High risk devices.

- Devices are classified as Class III if insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or that application of special controls described above would provide such assurance. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

- Class III devices generally require submission of a premarket approval (PMA) application.

8.2. Overview of Proposed Special Controls

Based on the safety and effectiveness information provided in the OSMA classification petition, as well as information gathered by the FDA, it is recommended that posterior cervical screw fixation systems be classified as class II devices, given that general and special controls appear to adequately mitigate the risks to health. The following special controls are proposed and discussed further in the sections below: labeling, training, conformance to material standards, biocompatibility, sterility, and mechanical testing. When evaluating the adequacy of the special controls, it is important to understand that the FDA correlates the ability of each special control identified to mitigate a given risk to health. The Agency also often relies on standards published through organizations like ASTM International and the International Standards Organization (ISO), in order to provide standard guides and methods for characterizing medical devices. The FDA Modernization Act of 1997 (FDAMA) (Pub. L. 105-115) amended section 514 of the FD&C Act to specifically authorize the Agency to recognize all or part of national and international standards as consensus standards for utilization by the Center for Devices and Radiological Health (CDRH). These standards can then be used across numerous manufacturers as a means for meaningful device comparison in 510(k) submissions for the purpose of establishing substantial equivalence.

8.2.1. Labeling

The following labeling recommendations are proposed in the OSMA petition:

- "Precaution: The implantation of cervical lateral mass and pedicle screw spinal systems should be performed only by experienced spinal surgeons with specific training in the use of this pedicle screw spinal system because this is a technically demanding procedure presenting a risk of serious injury to the patient."

- "Precaution: Pre-operative planning for implant of cervical lateral mass and pedicle screw implants should include review of radiographs, CT and/or MRI imaging to evaluate the patient's anatomy, transverse foramen and the course of the vertebral artery. If any findings would compromise the placement of lateral mass or pedicle screws, other surgical methods should be considered. In addition, use of intraoperative imaging should be considered to guide and/or verify device placement, as necessary."

- Labeling requirements presented in FDA guidance documents, including the *Device Labeling Guidance (#G91-1 (Blue Book Memo))*, which describes the contents of the label including indications, contraindications, precautions and warnings. The labeling for these devices includes the caution: Federal law restricts this device to sale by or on the order of a physician.

FDA generally agrees with the proposed labeling recommendations, but would propose to refine the labeling to require cross sectional imaging (i.e., CT and/or MRI) due to the unique risks in the cervical spine. The use of planar radiographs alone cannot provide the necessary imaging to mitigate the risk of improper screw placement. The panel will be asked to comment on this proposed labeling requirement.

8.2.2. Training

OSMA proposed using training and education, as provided by the major orthopedic and spinal societies as well as device manufacturers, as a special control.

FDA generally agrees with this recommendation, and adds that proper training and education provided by residency and fellowship training programs are also included. The Agency proposes that this training recommendation be a part of the device labeling to clearly describe the clinical training needed for the safe and effective use of these devices.

8.2.3. Conformance to Material Standards

The following standards were referenced in the OSMA petition as the materials used to manufacture posterior cervical screws:

- **ASTM F138-08** – Standard Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants
- **ASTM F67-06** – Standard Specification for Unalloyed Titanium, for Surgical Implant Applications
- **ASTM F1537-08** – Standard Specification for Wrought Cobalt-28Chromium-6Molybdenum Alloys for Surgical Implants

- **ASTM F136-08e1** – Standard Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications
- **ASTM F1295** – Standard Specification for Wrought Titanium-6 Aluminum-7 Niobium Alloy for Surgical Implant Applications

FDA agrees that materials standards are an appropriate special control to mitigate risks associated with the general biocompatibility of typical surgical implant materials.

8.2.4. Biocompatibility

The OSMA petition referenced ISO 10993: Biological Evaluation of Medical Devices as a method to assess biocompatibility of alternative or new materials.

FDA agrees that posterior cervical screw fixation systems must demonstrate the biocompatibility of the device material for its intended duration and contact (i.e., >30 days), but may not rely on ISO 10993 alone.

8.2.5. Sterility

While not included in the OSMA petition, sterilization validation testing must demonstrate the sterility of, or the ability to sterilize, the device components and any associated instruments with a sterility assurance level (SAL) of 1×10^{-6} using a sterilization cycle that has been validated in accordance with the quality system regulation (21 CFR Part 820).

FDA has included sterilization validation testing as a special control to mitigate the risk of infection.

8.2.6. Mechanical Testing

In vitro mechanical testing is recommended as a special control to mitigate some of the risks to health associated with the performance of these devices. As presented in the OSMA petition, there are three existing test standards, discussed below, that outline methods for mechanical testing of the cervical pedicle screw fixation systems that the Agency believes are applicable and appropriate to apply to mitigate some of the identified risks to health.

8.2.6.1. ASTM F1717

ASTM F1717: *Standard Test Methods for Spinal Implant Constructs in a Vertebrectomy Model*, discusses test methods for devices implanted on the anterior or posterior surfaces of the cervical, thoracolumbar, lumbar, or lumbosacral spine. For example, this standard focuses on testing spinal constructs for anterior cervical plating, pedicle screw, and anterolateral screw systems.

The following tests are proposed as special controls and are described in this CDRH recognized consensus standard:

- Static Compression Bending
- Static Torsion
- Static Tensile Bending
- Dynamic Compression Bending

The following results are suggested to be reported from this testing:

- Yield load or yield torque
- Yield displacement
- Elastic displacement or elastic angular displacement
- Ultimate load or ultimate torque
- Stiffness
- Fatigue life
- Failure modes

Additional Points:

- The ASTM F1717 standard does not outline a test method for dynamic torsion testing; however, based on the loading modes in the cervical spine, we do recommend this testing for posterior cervical fixation systems.

- The FDA may request mechanical testing not listed in the standard or a guidance document (e.g., shear, disassociation), depending on the technological characteristics of the spinal system.

The figures below show examples of test setups for cervical devices using this standard:

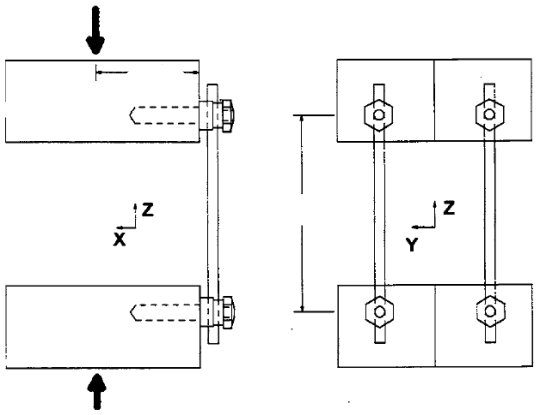

Figure 1. Standard Bilateral Construct Containing Screw, Rod and Screw[2]

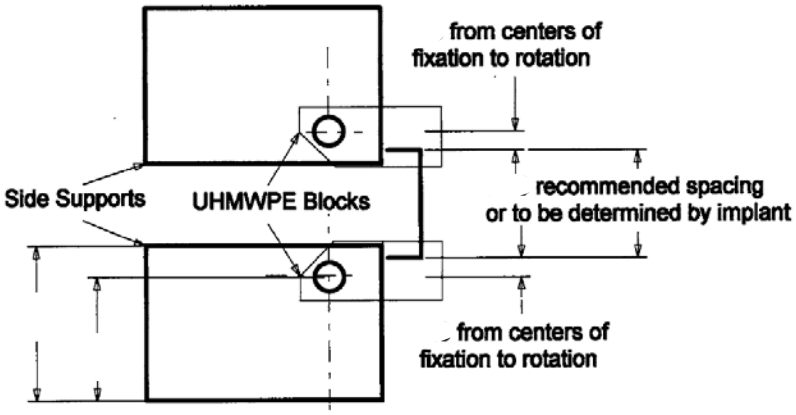

Figure 2. Cervical Bilateral Construct Test Setup for Screws or Bolts[2]

8.2.6.2. ASTM F2706

ASTM F 2706: *Occipital-Cervical and Occipital-Cervical-Thoracic Spinal Implant Constructs in a Vertebrectomy Model*, discusses test methods for devices implanted in the occipital-cervical (OC) and OCT spine. For example, this standard focuses on testing spinal constructs consisting of occipital plates, occipital screws, and thoracic pedicle screws. This standard would be considered worst-case in terms of proximal and distal fixation points in a construct that can span the entire cervical spine.

[2]Reprinted, with permission from ASTM F1717: Standard Test Methods for Spinal Implant Constructs in a Vertebrectomy Model, copyright ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428. A copy of the complete standard may be obtained from ASTM International, www.astm.org.

The following tests are proposed as special controls and are described in this CDRH recognized consensus standard:

- Static Compression Bending
- Static Tensile Bending
- Static Torsion
- Dynamic Compression Bending
- Dynamic Torsion

The following results are suggested to be reported from the testing:

- Yield load or yield torque
- Yield displacement
- Elastic displacement or elastic angular displacement
- Ultimate load or ultimate torque
- Stiffness
- Fatigue life
- Failure modes

The figures below show examples of test setups for OC and OCT devices using the standard:

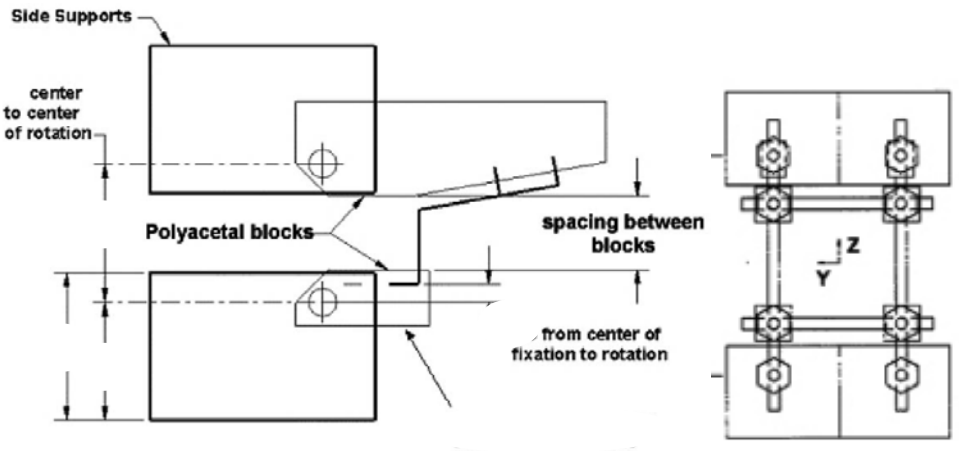

Figure 3. Occipital-Cervical Bilateral Construct Test Setup for Occipital Screws or Bolts (Left) and Cervico-Thoracic Bilateral Construct Test Setup (Right)[3]

8.2.6.3. ASTM F1798

ASTM F1798: *Standard Guide for Evaluating Static and Fatigue Properties of Interconnection Mechanisms and Subassemblies Used in Spinal Arthrodesis Implants*, discusses various ways to test spinal device components, specifically the interconnection mechanism between these

[3]Reprinted, with permission from ASTM F2706: Occipital-Cervical and Occipital-Cervical-Thoracic Spinal Implant Constructs in a Vertebrectomy Model, copyright ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428. A copy of the complete standard may be obtained from ASTM International, www.astm.org.

components. Examples of components tested in combination are screws, hooks, and rods.

The following tests are proposed as special controls and are described in this CDRH recognized consensus standard:

- Axial gripping
- Torsional gripping
- Flexion/extension
- Fatigue life or run-out to 2,500,000 cycles

The following results are suggested to be reported from the testing:

- Tightening torque
- Gripping capacity
- Yield load or moment
- Ultimate load or moment
- Loosening torque
- Failure mode

Additional Points:

- The FDA considers testing per ASTM F1798 to be useful for evaluating sub-components in spinal systems, especially in cases when modifications are being proposed to the components that may affect the interconnection mechanism(s).

- The FDA may request other sub-component testing not listed in this standard or a guidance document (e.g., cantilever), depending on the technological characteristics of the spinal system.

The figures below show examples of test setups for spinal components tested per the standard:

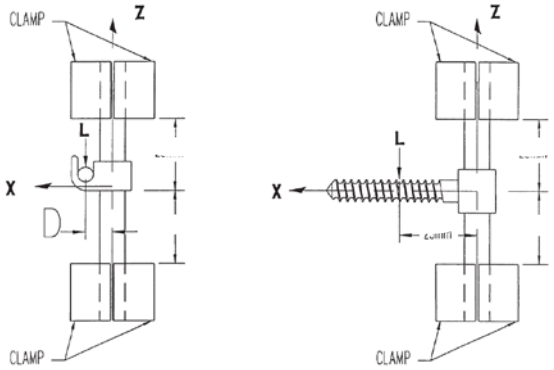

Figure 4. Flexion-Extension Moment Test Apparatus for Subassembly[4]

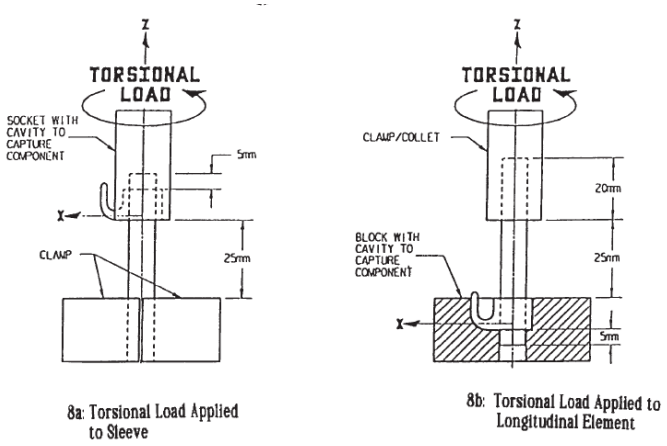

Figure 5. Torsional Load Applied to Sleeve (Left) and Torsional Load Applied to Longitudinal Element (Right) for Torsional Gripping Capacity Test[4]

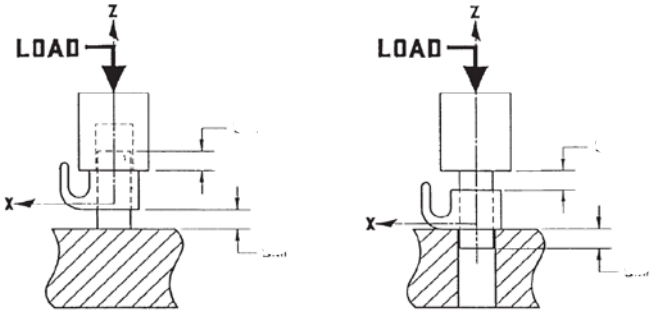

Figure 6. Load Applied to Sleeve (Left) and Load Applied to Longitudinal Element (Right) for Axial Gripping Capacity Test[4]

[4]Reprinted, with permission from ASTM F1798: Standard Guide for Evaluating Static and Fatigue Properties of Interconnection Mechanisms and Subassemblies Used in Spinal Arthrodesis Implants, copyright ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428. A copy of the complete standard may be obtained from ASTM International, www.astm.org.

FDA agrees that these mechanical testing standards are relevant and appropriate to assess static and dynamic characteristics of a given device and mitigate risks to health associated with the mechanical performance of cervical screw systems.

Overall, FDA agrees with the special controls proposed in the classification petition – labeling, training, biocompatibility, conformance to material standards, and mechanical testing. Sterilization validation was added as a standard special control relevant to all devices. Finally, FDA reserves the right to condense or expand these presented special controls, based on subsequent panel discussion and additional comments.

8.3. Literature Review of Mechanical Testing for Posterior Cervical Screw Systems

In the classification petition from OSMA, the sponsor excluded literature searches relating to pre-clinical studies associated with posterior cervical screw fixation systems. In July 2012, the FDA performed a search on bench studies for posterior cervical screw fixation systems to determine if any new safety or effectiveness information regarding biomechanical testing of the implants was presented in the scientific literature. A PubMed search was performed using the following terms: “cervical”[All Fields] AND ("spine"[MeSH Terms] OR "spine"[All Fields]) AND ("bone screws"[MeSH Terms] OR ("bone"[All Fields] AND "screws"[All Fields]) OR "bone screws"[All Fields] OR "screw"[All Fields]) AND ("biomechanics"[MeSH Terms] OR "biomechanics"[All Fields] OR "biomechanic"[All Fields]). Approximately 200 articles published from January 1999 to July 2012 were found. Articles were generally excluded for the following reasons: not available in English, computer modeling only, non-standard implantation or procedure methods, unique device features (e.g., bioresorbable), and/or otherwise not relevant to the subject devices and patient populations.

In summary, most studies demonstrated that posterior cervical screw fixation systems were able to provide adequate stability to the occipito-atlantoaxial (C1-C2) or subaxial (C3-C7) cervical spine using range of motion data captured through biomechanical testing of cadaveric specimens. These studies often compared ranges of motion of cervical pedicle or laminar screw fixation with anterior cervical plating systems (with or without interbody instrumentation) or other forms of posterior fixation such as cable, wiring, and hook techniques (Benke, 2010; Rhee, 2005). In many cases, posterior cervical screw fixation was found to be more rigid, thereby reducing the range of motion in the cervical spine compared to cable or hook techniques (Melcher, 2002; Henriques, 2000; Oda, 1999; Sutterlin, 2001). Other studies showed the ability of posterior screw fixation devices to provide stability of the cervical spine following multi-level corpectomies (Singh, 2003) where circumferential instrumentation often provided the most stability out of all constructs in these cases (Schmidt, 2003, 2010; Galler, 2007). For studies examining the occipitoatlantoaxial spine, some have shown that use of an occipital plate with cervical screw fixation significantly decreases the range of motion of the spine

(Nassos, 2009, Anderson, 2006; Oda 1999). Overall, the studies did not present any new safety or effectiveness information on posterior cervical screw fixation systems that was not already captured in this FDA Executive Summary or OSMA petition.

8.4. Mitigation of Risks to Health

The following list of risks was proposed in the OSMA petition and outline whether the special controls are adequate to mitigate risks to health associated with posterior cervical screw fixation systems. In general, the FDA agrees with the proposed risks and associated mitigation activities, with the exception of mechanical testing being used to mitigate the risk of implant loosening.

Table 5. Risks and Associated Mitigation Activities

Risks	Materials Standards	Mechanical Testing	Biocompatibility Standards	Training	Labeling	General Controls
Malposition				Yes	Yes	
Implant Loosening		~~Yes~~	Yes	Yes	Yes	
Device Breakage	Yes	Yes		Yes	Yes	Yes
Disassembly	Yes	Yes		Yes	Yes	
Malfunction– Device	Yes	Yes		Yes	Yes	Yes
Bone Fracture				Yes	Yes	
Graft Settling/ Displacement				Yes	Yes	
Loss of Correction	Yes	Yes	Yes	Yes	Yes	
Pseudarthrosis	Yes	Yes	Yes	Yes	Yes	
Bleeding/Vascular Injury				Yes	Yes	
Neurologic Injury				Yes	Yes	
CSF Leak				Yes	Yes	
Wound				Yes	Yes	
Infection				Yes	Yes	
Skin Irritation			Yes	Yes	Yes	
Cardiac				Yes	Yes	
Respiratory				Yes	Yes	
Revision Surgery	Yes	Yes	Yes	Yes	Yes	
Death	Yes	Yes	Yes	Yes	Yes	

FDA generally agrees with the proposed risk mitigation activities. Of particular note, FDA agrees that a number of risks can be mitigated with mechanical testing; however, the Agency disagrees that implant loosening (such as screw loosening at the bone/implant interface) can be adequately captured via in vitro testing because this type of fatigue behavior is difficult to assess on the bench. However, there is clinical evidence showing high fusion rates with posterior cervical screw fixation. As such, we believe the current body of clinical evidence shows that the other proposed special controls mitigate the risk of implant loosening.

The panel will be asked to discuss the following regarding the device-related risks to health and the proposed special controls designed to mitigate these risks:

1. ***the completeness of the stated risks to health, as described above in Table 5, and***
2. ***the adequacy of the proposed special controls in assessing the risks to health associated with posterior cervical screw fixation systems.***

9. Summary

For the purposes of classification, FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. the persons for whose use the device is represented or intended;

2. the conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. the probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. the reliability of the device.

Part (g)(1) of this regulation further states that it "is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into class III."

9.1. Special Controls

The petitioner has proposed special controls (see Section 8 above) to be enacted in conjunction with the proposed classification. These include conformance to materials and biocompatibility standards as well as recommendations for device labeling and surgeon training. Performance bench testing per ASTM F1717, ASTM F2706, and

ASTM F1798 has also been proposed as a special control to mitigate certain risks to health to assess device characteristics in determining substantial equivalence. The FDA has also recommended the addition of sterilization validation as a special control.

9.2. Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

9.3. Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

FDA believes that the available scientific evidence supports a class II determination because the data does support a reasonable assurance of safety and effectiveness, the proposed special controls would be sufficient to provide such assurance, and there is not an unreasonable risk of illness or injury.

Based on the available scientific evidence and proposed special controls, the panel will be asked whether a designation of class II is appropriate for posterior cervical screw fixation for the indications described above in Section 3.

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11. Appendix A: OSMA Petition

12. Appendix B: Data Abstraction Table for Pediatric Literature Review

13. Appendix C: FDA Supplemental Literature Articles